Pyrimidine annelated heterocycles—synthesis and cycloaddition of the first pyrimido[1,4]diazepine *N*-oxides

Frances Heaney,*[a] Cathriona Burke,[b] Desmond Cunningham[b] and Patrick McArdle[b]

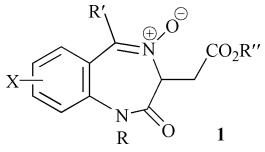
[a] *Department of Chemistry, The National University of Ireland, Maynooth, Ireland*
[b] *Department of Chemistry, The National University of Ireland, Galway, Ireland*

Received (in Cambridge, UK) 5th September 2000, Accepted 23rd January 2001
First published as an Advance Article on the web 27th February 2001

5-Formyl- and 5-acetyl-4-(alkenylamino)pyrimidines **5** have been prepared as precursors to novel pyrimido[1,4]-diazepine *N*-oxides **3**. In addition to cyclisation to the targeted dipoles the substrates **5** have also been observed to form imidazopyrimidines **12** and **39** *via* an intramolecular Michael addition; additionally **5b** has been observed to form the pyrimidoazepinone **42**. Aldonitrone **3a** cycloadded readily to olefinic dipolarophiles; ketodipole **3b** did not share this reactivity. Both dipoles reacted with acetylenic dipolarophiles but the ensuing cycloadducts **37** were unstable; facile ring contraction of their isoxazolopyrimidodiazepine skeletons to the pteridine nucleus is noted. The structure of **37c** has been determined by X-ray crystallography.

Introduction

Pyrimidines and their ring fused derivatives have a broad spectrum of biological activity; best known as the heterocyclic core of the nucleic acid bases, these ring systems are often incorporated into drugs designed for cancer and anti-viral treatment.[1] We have been investigating the preparation and cycloaddition potential of 1,4-benzodiazepinone *N*-oxides[2] **1**



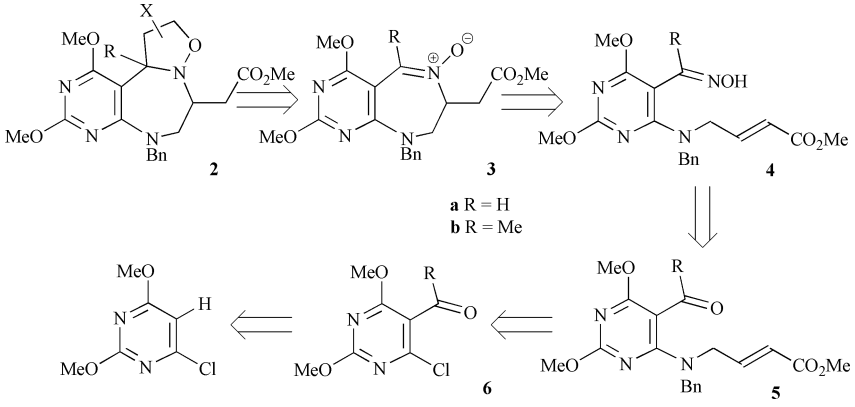
1

and more recently have turned our attention to a hitherto unknown series of pyrimidine compounds, the isoxazolo-pyrimidodiazepines **2**. 8,9-Dihydro-7*H*-pyrimido[4,5-*e*][1,4]-diazepine N^6-oxides, **3**, were the target nitrones and their synthesis from (alkenylamino)pyrimidines **5** was envisaged (Scheme 1). Similar substrates have been widely investigated by Noguchi's group in their comprehensive study of the preparation of fused azepine rings by intramolecular thermal ene reactions (carbonyl, imine or hydrazone).[3] In a recent communication we reported that the preparation of compounds like **5** from a condensation reaction of a secondary amine with a chloropyrimidine proceeded in high yield only when the amino component did not carry an α-substituent.[4]

Results and discussion

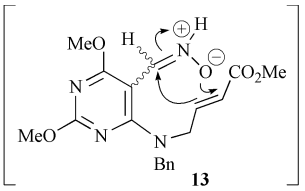
The general approach to the preparation of γ-aminocrotonates related to **7** involves nucleophilic displacement of an allylic halide or nosylate (*p*-nitrobenzenesulfonate) from the appropriate crotonate.[5] The amine **7** was prepared from reaction of methyl 4-bromobut-2-enoate with benzylamine. The identity of the reaction product is sensitive to the experimental conditions. With an equimolar ratio of reactants the *N*,*N*-bisalkylated compound **8** is the major product (69%); moderate yields of the corresponding diesters were obtained by Rahman and co-workers[6] on reaction of primary alkyl amines with the same bromobutenoate. The optimal yield of **7** (65%) was obtained following reaction with three equivalents of benzylamine (Et_2O, 0 °C). With a large excess of benzylamine, 10 equivalents, the 4-aminopyrrolidinone **9** resulted (100%). The lactam likely arises from **7** in two steps, *viz*. an initial Michael type addition of a second molecule of $BnNH_2$, giving **10**, followed by a 5-*exo*-*trig* cyclisation. Alternatively **10** may arise from **7** *via* an initial shift of the amino group from the external to the internal position by way of an aziridine intermediate, **11** and ring opening by amine attack at the less substituted ring carbon[7] (Scheme 2).

The condensation between the allylic amine **7** and the

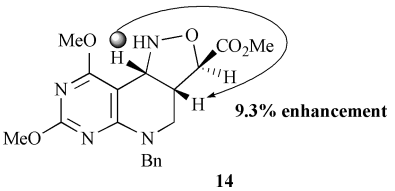


Scheme 1

 DOI: 10.1039/b007163n

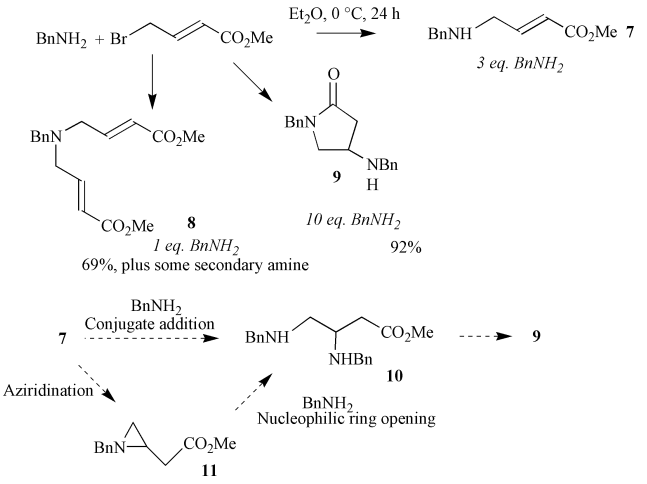


13



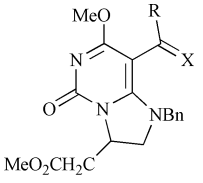
14

Fig. 1



Scheme 2

chloropyrimidine **6a** furnished **5a** in high yield (78%) following stirring in $CHCl_3$ at rt in the presence of triethylamine. We anticipated a straightforward carbonyl to oxime functionalisation on reaction of **5a** with NH_2OH, however a number of products resulted from this reaction. The starting aldehyde **5a** and the proposed oxime **4a** both have a high density of functionality and imidazopyrimidines **12a**,**b** can arise from these



12

a R = H, X = O
b R = H, X = NOH
c R = Me, X = O

substrates by cyclisation of the nucleophilic pyrimidine nitrogen atom onto the pendant electrophilic alkene.[4] The oxime **4** has two further channels for reactivity, *viz*. tautomerisation to the corresponding *NH*-dipole **13** with subsequent cycloaddition to **14** [*i*ntramolecular *o*xime *o*lefin *c*ycloaddition, IOOC, Fig. 1],[8] or 7-*exo*-*trig* cyclisation to the targeted pyrimidodiazepine *N*-oxide **3a** [*aza*protio cyclo*t*ransfer reaction, APT,[9] Fig. 2]. The conditions best disposed to nitrone formation employed MeOH at 0 °C, whence **3a** was isolated in 65% yield accompanied by 14% of the tricyclic isoxazolopyridopyrimidine **14** [IOOC product], 5% of the imidazopyrimidine **12a** and 5% of the corresponding oxime **12b**.

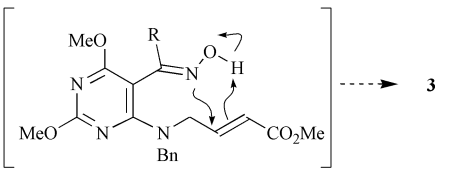
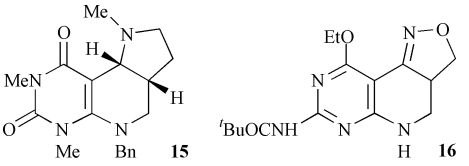
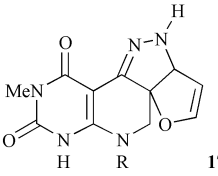


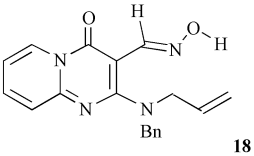
Fig. 2

The isoxazolopyridopyrimidine **14** is furnished diastereospecifically and has *cis* ring junction stereochemistry as indicated by both coupling constant [$J_{9b,3a}$ 6.01 Hz], and nuclear Overhauser enhancement difference spectroscopy results (NOEDS), summarised in Fig. 1]. Intramolecular cycloaddition of related azomethine ylides, nitrile oxides and nitrile imines giving 5,6,6-ring systems, pyrrolo- **15**, isoxazolo- **16** and

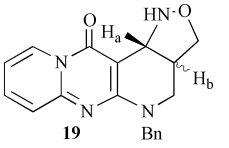




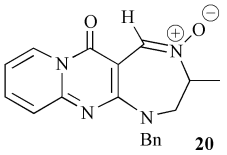
pyrazolo-pyridopyrimidines **17** have been reported.[10] In a closer parallel Noguchi has demonstrated, and afforded a mechanistic proposal for, an IOOC reaction of a pyrido[1,2-*a*]pyrimidine system,[8e] *e.g.* the oxime **18** upon heating in EtOH afforded the



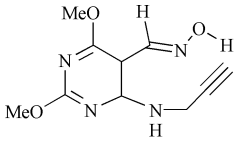
18



a *cis*-ring junction [$J_{a,b}$ 6.2 Hz]
b *trans*-ring junction [$J_{a,b}$ 11.2 Hz]



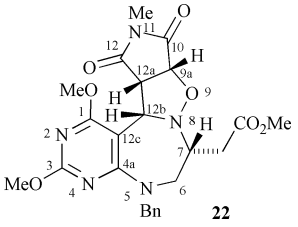
tetracycle **19a** in 93% yield; when the reaction solvent was changed to C_6H_6 diastereomeric adducts **19a**,**b** (76% and 14% yield respectively) were obtained together with the tricyclic *N*-oxide **20** (8%). The product distribution with Noguchi's substrate differs significantly from ours; the low yield of the dipole and the absence of any imidazo fused adducts is a consequence of the electronically neutral pendant double bond in **18**. The corresponding centre in **4a** carries a methoxycarbonyl substituent which facilitates nucleophilic attack by the oxime or pyrimidine nitrogen atoms furnishing dipole **3a** and imidazopyrimidines **12a/b** respectively. In keeping with the requirement for a high degree of electrophilicity at the unsaturated centre it is perhaps not surprising that the terminally unsubstituted alkynyl substrate **21** failed to partake in any ring forming reactions. After several hours heating alone or in the presence of $AgBF_4$ **21** was returned unchanged. The nitrone forming power of the intramolecular oxime–alkyne cyclisation reaction has been demonstrated thermally for 6-membered dipoles[11] and Ag(I) catalysed oxime–allene cyclisation leading to 5- and 6-membered nitrones has been reported.[12] The cyclisation of **21**



21

has both electronic and geometrical disadvantages when compared with substrates like **4** and thus has a prohibitively high activation energy.

Cycloaddition of nitrone **3a** to *N*-methylmaleimide (THF, rt, 24 h) proceeded with high diastereofacial selectivity; the major adduct **22** was isolated in 73% yield and a second isomer too



22

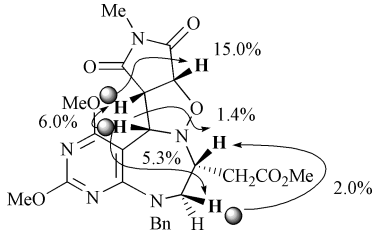
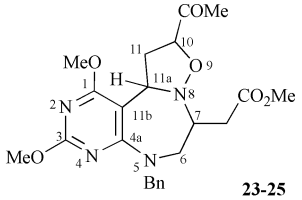


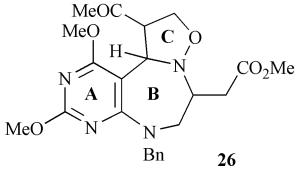
Fig. 3 NOEDS results for compound **22**.

small in quantity to be isolated was seen in the ^{1}H NMR spectrum of the crude reaction mixture. The relative stereochemistry of **22**, the first example of this ring system, is tentatively assigned as shown following NOEDS experiments; the pertinent results are summarised in Fig. 3. That the 12a- and 12b-protons are *cis* is evident from their mutual enhancement upon irradiation of each other (~6%). On its own the small enhancement (~1%) on 7-H following irradiation of 12b-H is insufficient to confidently assign these protons as being *cis*-orientated; however this proposal is indirectly supported by the following enhancements: 12b-H to 6-H (~5%) and 6-H to 7-H (~2%). The tetracyclic skeleton of **22** thus arises from a transition state involving an *endo*-addition of the dipolarophile to the face of the dipole carrying the CH_2CO_2Me substituent.

Cycloaddition to monosubstituted olefinic dipolarophiles progressed in much poorer chemical yield and showed varying degrees of selectivity. On reaction of **3a** with methyl vinyl ketone four adducts, **23**–**26**, were isolated in 23, 12, 18 and 41% yields respectively (based on 53% conversion of nitrone). The first three, **23**–**25**, are stereoisomeric adducts with the acyl sub-



23-25



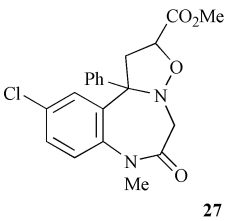
26

Table 1 ^{13}C Resonance position for the methylenic carbon atoms in the adducts **23**–**26**

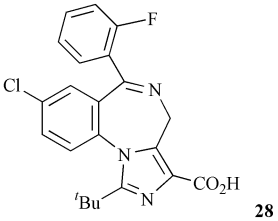
Adduct (NMR solvent)	CH_2 on isoxazolidine ring	NCH_2Ph	C-6	CH_2CO_2Me
23 ($CDCl_3$)	39.23	53.50	52.95	33.44
24 ($CDCl_3$)	42.80	54.43	52.94	36.76
25 ($CDCl_3$)	42.23	53.81	50.46	36.83
26 (C_6D_6)	67.85	54.33	50.00	36.87

stituent in the 5-position of the isoxazolidine ring and the major adduct **26** is a "4-substituted" regioisomer. The regiochemical assignments are easily made following analysis of the ^{13}C DEPT 135 spectrum. The adducts have four methylene groups in total; three of these, NCH_2Ph, C-6 and CH_2CO_2Me, are common to all the adducts and their ^{13}C resonance positions are similar (Table 1). For any "5-substituted" isoxazolidines the fourth methylene carbon is C-11 and it has two directly attached carbon atoms. The final methylene carbon atom of "4-substituted" adducts is C-10. It has neighbouring oxygen and carbon atoms; consequently it is deshielded with respect to C-11 in the regioisomeric compounds.

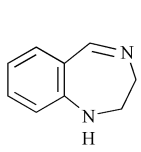
Unfortunately the ^{1}H NMR data of the adducts **23**–**26** are not good enough to permit discrimination between the possible diastereomeric structures. For the major adduct, **26**, with the exception of the methoxy and the aryl protons, all the resonance signals in the ^{1}H NMR spectrum recorded at rt appeared broad. When the spectrum was recorded with a probe temperature of −19.9 °C the signals sharpened to reveal the expected multiplicities. It is thus apparent that the adduct enjoys a degree of conformational mobility at rt which is removed on cooling to ~−20 °C. A Dreiding scale model of the tricyclic framework of **26** indicates significant flexibility; the diazepine ring easily flips between the boat and various half chair conformations and there is also some opportunity for ring inversion of the isoxazolidine nucleus. Molecular modelling and/or NMR analyses have been performed on skeleta related to **26**, *e.g.* isoxazolo[2,3-*d*]-[1,4]benzodiazepinone **27**,[13a] imidazo[1,5-*a*][1,4]benzodiazepine



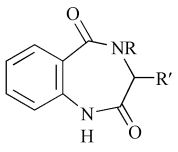
27



28



29



30

28,[13b] 2,3-dihydro-1*H*-1,4-benzodiazepine **29** [13c] and 1,4-benzodiazepine-2,5-diones **30**,[13d] however no systematic study has been reported for tricycles like **26** which have a higher degree of saturation in the B and C rings.

After 3 d stirring at rt in THF with phenyl vinyl sulfone 61% of nitrone **3a** was converted into two diastereoisomeric "4-substituted" cycloadducts. The regiochemical assignments are again based on the ^{13}C resonance position of the isoxazolidine ring methylene group (~66 ppm in both cases). Efforts to assign the relative stereochemistry of these adducts from NOEDS data failed. The major adduct **31** (57%) has key resonance signals (10-H, 10′-H, 11-H) coincident in both $CDCl_3$ and

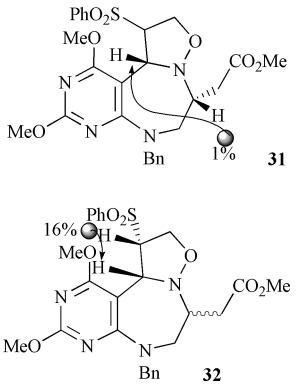
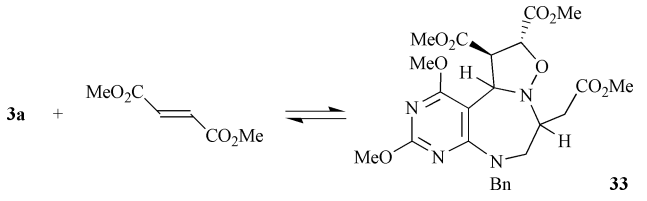


Fig. 4 NOEDS results for compounds **31** and **32**.

C_6D_6. Irradiation of the signal representing 7-H ($CDCl_3$) caused a ~1% enhancement on the signal for 11a-H (reciprocated on back irradiation of 11a-H) (Fig. 4). Since the tricycle has conformational freedom it is difficult to correlate the small cross ring enhancement with a *cis*-relationship between these protons; however this value is very similar to that observed for the maleimide adduct **22** where the corresponding protons were indirectly shown to be in close proximity. The minor adduct **32** (34%) has limited stability in $CDCl_3$, consequently spectra were recorded in C_6D_6; unfortunately in this solvent 10-H and 7-H were coincident, prohibiting any chance to ascertain the cross ring stereochemistry. Irradiation of the signal representing 11-H caused a ~16% enhancement on the signal for 11a-H; this adduct therefore results from an *endo* addition of phenyl vinyl sulfone to one face of the dipole.

Dimethyl fumarate was expected to be a good candidate for cycloaddition with **3a**,[14] accordingly these components were



stirred in THF at rt. Reaction progress was monitored by TLC and appeared to progress toward cycloadduct formation. However, following chromatographic separation (SiO_2, Et_2O, petroleum ether), ^1H NMR ($CDCl_3$) analysis of the fractions considered as pure cycloaddition product indicated the presence of three compounds: cycloadduct **33** as well as starting nitrone and dimethyl fumarate. Evidently the adduct is quite unstable and retrocycloaddition begins almost immediately in $CDCl_3$ and is complete on standing at rt for 3 d. Varying degrees of instability are noted in other deuterated solvents (C_6D_6, THF-d_8, CD_3CN, acetone-d_6, toluene-d_8). Repulsive steric interactions are likely responsible for the instability of **33** which has a greater degree of substitution than the adducts previously discussed. High cycloreversion rates for adducts of cyclic nitrones with dimethyl fumarate/maleate have been noted previously, *e.g.* in studues by Gandolfi and co-workers with dihydroisoquinoline *N*-oxide **34** equilibrium was established between the diastereomeric cycloadducts **35** and **36**;[15] for our more highly substituted dipole equilibrium is between cycloadduct and reactants. The reaction of **3a** with fumarate was repeated, firstly on an analytical scale at rt in acetone (slowest retrocycloaddition rate) with an excess of one reactant (fumarate, 10 equivalents) and progress was followed by HPLC. Enhancement of intensity of the signal occurred due to product stabilised after 27 h stirring. An independent HPLC measurement showed the position of the equilibrium to be sensitive to temperature, with lower temperatures (4 °C) favouring cycloadduct. On scale-up a fresh sample of **33** was isolated and ^1H

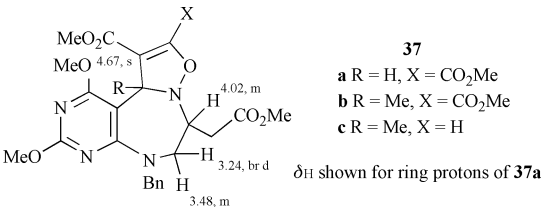


Fig. 5

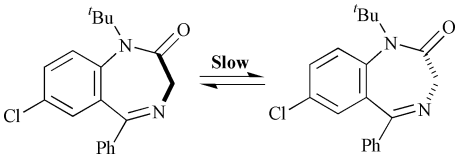
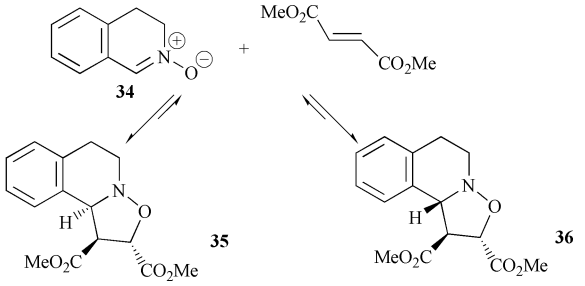


Fig. 6

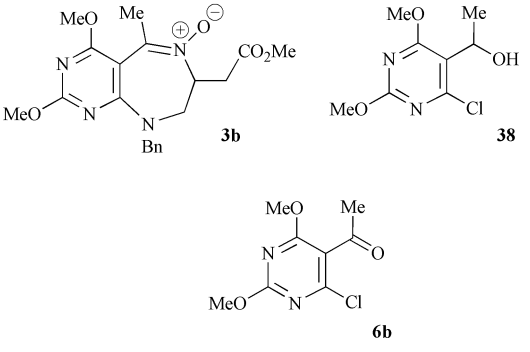


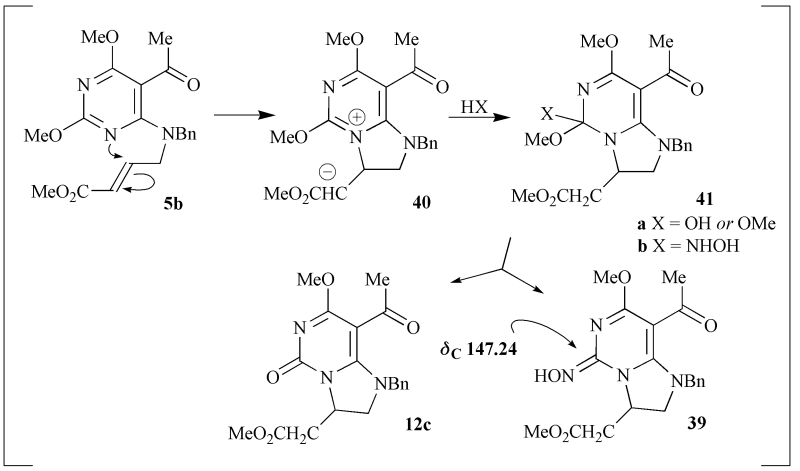
NMR spectra were recorded in toluene-d_8 at −60 °C. In addition to resonance signals characteristic of the tricycle the spectrum showed a small number of signals (of low intensity) not immediately attributable to cycloadduct or its precursors. It is plausible that these "additional" signals represent a minor conformer ("hidden partner") of the tricyclic framework.[13]

Reaction of **3a** with dimethyl acetylenedicarboxylate in THF at 0 °C (24 h) led to a number of new compounds. Attempts to separate the crude material by flash chromatography further increased the complexity of the mixture and only a small amount (7%) of cycloadduct was isolated. ^1H NMR analysis of this material shows resonance signals characteristic of the protons of **37a** (Fig. 5). A second product, isolated in 10% yield, was later identified as the pteridine **43**. In common with most 4-isoxazolines[16] **37a** is rather unstable and it readily decomposed. Examination of the components of thermal decomposition showed **37a** to be a precursor of **43**.

The presence of a methyl substituent at the *C*-position of the dipole **3** is likely to exert modest steric demands and could be expected to influence the reactivity, regio- and stereoselectivity of any cycloaddition reactions. Further, the presence of such a substituent will influence the conformational properties of the ensuing cycloadducts. Gilman and co-workers have reported that the introduction of a Bu′ group at the N-1 position of diazepam effectively inhibits conformational racemisation and synthesis of each enantiomer becomes possible[17] (Fig. 6).

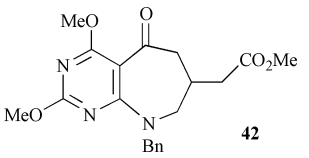
The ketodipole **3b** has been prepared by a reaction sequence parallel to that described for the aldonitrone **3a**. The acyl-





Scheme 3

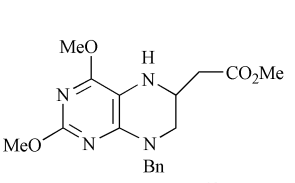
pyrimidine **6b** resulted from PCC oxidation of the alcohol **38** (87%), itself prepared from commercially available 6-chloro-2,4-dimethoxypyrimidine. Condensation of **6b** with **7** gave **5b** in 82% yield. Treatment of **5b** with NH_2OH was expected to furnish **3b** *via* an oximation–cyclisation sequence. However imidazopyrimidine formation competed and **12c** and **39** were isolated together with nitrone. A key feature in distinguishing between the two imidazopyrimidines is the ^{13}C resonance position of the C-5 carbon atom; in **12c** this is an "oxo" carbon and resonates at ~155 ppm whilst in **39** this position is an "hydroxyimino" carbon and it resonates at ~147 ppm. Further the mass spectrum of **39** has molecular ion at 387. In the *best* experiment both base and hydroxylamine hydrochloride were used in excess; pyridine was employed as the reaction solvent and a five-fold excess of $NH_2OH{\cdot}HCl$ was used (rt, 48 h). These conditions furnished nitrone **3b** (49%) as well as imidazopyrimidines **12c** (25%) and **39** (24%). Reaction in MeOH with pyridine as base (rt, 24 h) gave the dipole **3b** (12%) and the 5-oxoimidazopyrimidine **12c** (65%) as the only products whilst a MeOH, $NaHCO_3$ combination (rt, 72 h) gave nitrone **3b** (41%) and the 5-(hydroxyimino)imidazopyrimidine **39** (52%). In MeOH pyridine functions as a homogeneous base whilst $NaHCO_3$ will remain a solid; this difference and their different pK_a values [pyridine 5.25 and $NaHCO_3$ 6.35] may influence the pH of the reaction medium and the availability of free NH_2OH for reaction and so account for the different product distribution. Thus **12c**, the dominant product from reaction using an (approximately) equimolar quantity of pyridine does not require NH_2OH for its formation whilst the generation of both **3b** and **39**, the products of reaction employing $NaHCO_3$ as base, does involve NH_2OH. A plausible origin of **12c** and **39** is summarised in Scheme 3. The different products are likely a consequence of the nature of the attacking species—H_2O, MeOH or NH_2OH—on the intermediate zwitterion **40** with **41a** being the precursor to **12c** and **41b** leading to **39**. Finally when **5b** was heated alone in MeOH the pyrimidoazepinone **42** (74%) and the 5-oxoimidazopyrimidine **12c** (25%) were formed. Presumably **42** arises *via* Michael attack of the enolate of **5b** onto



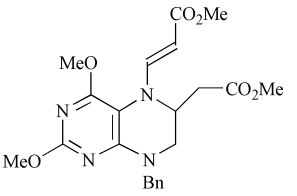
42

the internal double bond with the tertiary amine functionality behaving as base (either inter- or intramolecularly); its formation indicates yet another available reaction path for this densely functionalised substrate. Pyrimido[4,5-*b*]azepin-5-ones have previously been considered as potentially interesting synthetic intermediates in the preparation of folic acid derivatives.[18]

The keto dipole **3b** failed to cycloadd to any of *N*-methylmaleimide, methyl vinyl ketone, dimethyl fumarate/maleate or phenyl vinyl sulfone, returning unchanged starting materials after stirring at elevated temperatures. However it did react with acetylenic substrates, methyl propiolate and dimethyl acetylenedicarboxylate. The reaction of **3b** with dimethyl acetylenedicarboxylate after 72 h stirring in THF yielded only a small sample of one cycloadduct (6%); ^1H NMR data supports its assignment as **37b** and due to the instability of the cycloadduct no further analytical data could be acquired. The major product was characterised as the pteridine **43** (47%). If **37b** is heated alone in boiling MeOH quantitative conversion to **43** occurs after 2 h.



43



44

On stirring **3b** at rt (24 h) with excess methyl propiolate (as solvent and reactant) three new products, the "4-substituted" isoxazoline, **37c** (42%), the *NH*- **43** (17%) and the *N*-substituted **44** (23%) pteridines, were formed. Full characterisation of the primary cycloadduct, **37c**, by NMR spectroscopy proved impossible as decomposition took place in $CDCl_3$ during the time span required for acquisition of ^{13}C data. However, the adduct was stable in the solid phase and crystals suitable for X-ray analysis were obtained from petroleum ether–Et_2O. The ORTEX drawing of **37c** (Fig. 7), shows the tricyclic skeleton to adopt the folded rather than the extended conformation.[13a] The hydrogen on C(9) and the methyl group on C(10) are on the same side of the fused ring system. However the molecule is not flat at the fusion point with the C(20)–C(10)–N(2)–C(9) dihedral angle being 91°. The hydrogen atom on C(9) is 4.158 Å from the mean of the hydrogens on the methyl group. This interproton distance is close to the limit for detection of nuclear Overhauser effects. That the tricycle **37c** is the precursor of the *NH*-pteridine has been illustrated; thus simply heating **37c** alone in boiling MeOH furnishes **43** in 95% yield. That the *N*-substituted pteridine **44** arises from the unsubstituted parent by a *pseudo* Michael addition reaction to a molecule of methyl propiolate was also verified by an independent experiment. The pteridine nucleus is the product of a thermal ring contraction of the isoxazolopyrimidodiazepine skeleton and the rearrangement of **37c** likely follows the mechanism suggested by Freeman

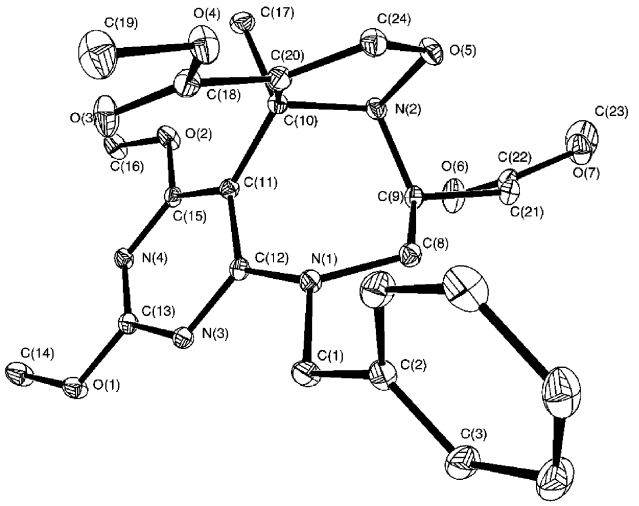
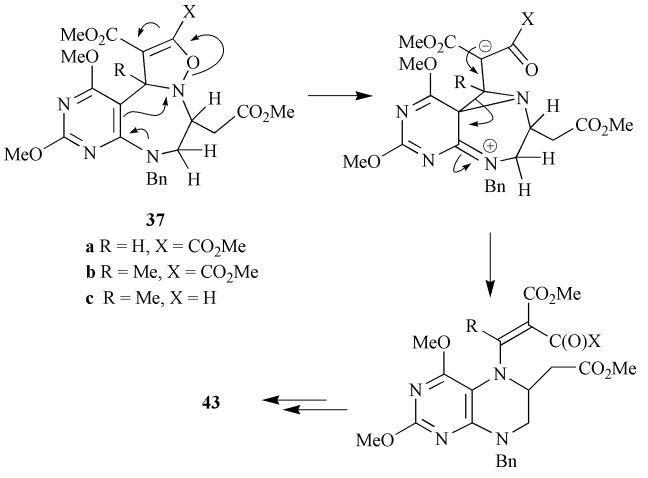


Fig. 7 ORTEX Drawing of **37c**. Crystallographic numbering system shown.

and co-workers for isoxazolobenzodiazepines, involving a 1,2-carbon-to-nitrogen shift followed by cleavage of the N–O bond of the isoxazoline ring[19] as outlined in Scheme 4. An



Scheme 4

analogous rearrangement explains the formation of **43** from **37a**,**b**.

Pteridines, being widely distributed in nature, are of general interest due to their potential biological activity. They are most commonly synthesised starting from a condensation reaction of a 5,6-diaminopyrimidine (Gabriel–Isay reaction or modification of) or much less commonly from a pyrazine nucleus;[20] their preparation by transformation of other heterocyclic rings is much less common. This is the first example of a pteridine synthesis by ring contraction of an isoxazolopyrimidodiazepine.

Conclusion

Pyrimido[1,4]diazepine *N*-oxides have been prepared for the first time and the cycloadditive ability of **3** has been shown to be dependent on the degree of substitution at the C-atom of the dipole. The aldonitrone **3a** reacts with both olefinic and acetylenic substrates whilst the *C*-substituted dipole **3b** is inactive to olefinic dipolarophiles. With monosubstituted olefins **3a** displays a preference for formation of 4-substituted isoxazolidine rings. The diastereoselectivity of the cycloaddition is lowest with methyl vinyl ketone and highest with *N*-methylmaleimide. The dimethyl fumarate cycloaddition product had a short lifetime at rt and underwent retrocycloaddition to exist in equilibrium with the starting nitrone **3a** and dipolarophile. Both dipoles react with acetylenic substrates but the primary adducts have a low degree of stability and readily rearrange to the pteridine nucleus. This ring contraction may be a useful route to synthesis of unusually substituted pteridines.

Experimental

Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer model 240 CHN analyser. NMR spectra were recorded using a JEOL JNM-LA400FT NMR instrument operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C nuclei with tetramethylsilane as internal reference; *J* values are given in Hz. Mass spectroscopy was performed on a Profile Kratos Analytical Instrument. Flash chromatography was carried out on silica gel (200–400 mesh; Kieselgel 60, E. Merck) with air pump pressure. Analytical TLC plates were purchased from Merck. Samples were located by UV illumination using a portable Spectroline Hanovia lamp ($\lambda = 254$ nm) or by the use of iodine staining. All solvents used were purified by standard procedures and petroleum ether refers to fractions of light petroleum boiling between 40–60 °C.

Methyl (*E*)-4-(benzylamino)but-2-enoate 7, methyl (*E*)-4-{benzyl[(*E*)-4-methoxy-4-oxobut-2-enyl]amino}but-2-enoate 8 and 1-benzyl-4-(benzylamino)pyrrolidin-2-one 9

A solution of methyl 4-bromocrotonate (1.00 g, 5.6 mmol) in Et_2O (3 cm^3) was added slowly to a solution of benzylamine (10 equivalents, 6.0 g, 56 mmol) in Et_2O (20 cm^3) at 0 °C. The resulting mixture was stirred at 0 °C for 24 h, then concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 cm^3), washed with brine (3 × 50 cm^3), dried over Na_2SO_4 and reconcentrated under reduced pressure. Purification by flash chromatography (Et_2O–petroleum ether 1 : 1) afforded three pure products, which are listed in order of elution. Tertiary amine **8**, a white solid (0.16 g, 10%), mp 66–67 °C (Et_2O, petroleum ether) (Found C, 67.31; H, 6.61; N, 4.76. $C_{17}H_{21}NO_4$ requires C, 67.25; H, 6.92; N, 4.62%); δ_H: 7.19 (5H, m, Ar-H), 6.88 (2H, m, 2′-H, 3-H), 5.97 (2H, dt, *J* 15.74 and 1.83, 3′-H, 2-H), 3.65 (6H, s, OCH_3, OCH_3), 3.52 (2H, s, CH_2Ph), 3.14 (4H, dd, *J* 5.86 and 1.83, 1-H, 1′-H, 4-H, 4′-H); δ_C: 166.65 (CO_2CH_3, CO_2CH_3), 145.97 (2′-C, 3-C), 138.33 (Ar-C), 128.60, 127.48, 127.33 (Ar-CH), 122.70 (2-C, 3′-C), 58.42 (CH_2Ph), 54.51 (1′-C, 4-C), 51.52 (CO_2CH_3, CO_2CH_3); secondary amine **7**, a yellow oil (0.74 g, 65%) (Found C, 69.86; H, 6.89; N, 6.78. $C_{12}H_{15}NO_2$ requires C, 70.24; H, 7.32; N, 6.83%); δ_H: 7.36 (5H, m, Ar-H), 7.02 (1H, m, 3-H), 6.03 (1H, dt, *J* 15.74 and 1.83, 2-H), 3.80 (2H, s, CH_2Ph), 3.74 (3H, s, OCH_3), 3.42 (2H, dd, *J* 5.13 and 1.83, 4-H, 4′-H); δ_C: 166.76 (CO_2CH_3), 146.89 (3-C), 139.63 (Ar-C), 128.33, 127.99, 127.02 (Ar-CH), 121.03 (2-C), 53.10 (CH_2Ph), 51.40 (CO_2CH_3), 49.32 (4-C); lactam **9**, a brown oil (0.31 g, 20%) (Found C, 77.46; H, 7.23; N, 9.76. $C_{18}H_{20}N_2O$ requires C, 77.11; H, 7.19; N, 9.99%); δ_H: 7.28 (10H, m, Ar-H), 4.47 (2H, d, *J* 2.20, NHCH_2Ph), 3.71 (2H, d, *J* 2.93, NCH_2Ph), 3.44 (2H, m, 4-H, 5-H), 3.07 (1H, dd, *J* 9.52 and 4.03, 5′-H), 2.69 (1H, dd, *J* 16.84 and 7.69, 3-H), 2.32 (1H, dd, *J* 16.84 and 5.13, 3′-H), 1.84 (1H, br s, NH); δ_C: 172.96 (C-2), 139.33 (Ar-C), 136.10 (Ar-C), 128.59, 128.42, 127.99, 127.48, 127.14 (Ar-CH), 52.93 (C-4), 51.52 (NHCH_2Ph), 50.21 (C-3), 43.22 (NCH_2Ph), 38.70 (C-4).

Methyl (*E*)-4-[benzyl(5-formyl-2,6-dimethoxypyrimidin-4-yl)-amino]but-2-enoate, 5a

To a stirred solution of 4-chloro-5-formyl-2,6-dimethoxypyrimidine[21] (1.65 g, 8.13 mmol) in $CHCl_3$ (15 cm^3), **7** (2.00 g, 8.13 mmol) and triethylamine (0.82 g, 8.13 mmol) were added at 0 °C. The reaction mixture was warmed to rt and stirring continued for 10 h. The crude mixture was washed with brine (3 × 50 cm^3), dried over anhydrous Na_2SO_4 and concentrated

under reduced pressure. Crystallisation (petroleum ether, Et_2O) afforded the title product, **5a**, a white solid (2.30 g, 78%), mp 79–80 °C (Et_2O, petroleum ether) (Found C, 61.44; H, 5.53; N, 11.16. $C_{19}H_{21}N_3O_5$ requires C, 61.46; H, 5.66; N, 11.32%); δ_H: 10.06 (1H, s, CHO), 7.25 (5H, m, Ar-H), 6.74 (1H, dt, *J* 16.10 and 5.37, 3′-H), 5.87 (1H, d, *J* 16.10, 2′-H), 4.76 (2H, s, C*H*$_2$Ph), 4.26 (2H, d, *J* 5.37, 4-H, 4′-H), 4.05 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 3.72 (3H, s, CO_2CH_3); δ_C: 184.91 (CHO), 175.26 (C-2), 166.31 (*C*O_2CH_3), 165.05 (C-6), 164.34 (C-4), 143.61 (C-3′), 136.50 (Ar-C), 128.67, 127.58, 122.71 (Ar-CH), 127.71 (C-2′), 97.05 (C-5), 54.95 (OCH_3), 54.75 (OCH_3), 54.70 (*C*H_2Ph), 51.59 (CO_2CH_3), 50.90 (C-4′).

9-Benzyl-2,4-dimethoxy-7-(2-methoxy-2-oxoethyl)-8,9-dihydro-7*H*-pyrimido[4,5-*e*][1,4]diazepin-6-ium-6-olate 3a

A solution of **5a** (100 mg, 0.27 mmol), $NH_2OH{\cdot}HCl$ (22.5 mg, 0.32 mmol) and pyridine (25.6 mg, 0.03 cm^3, 0.32 mmol) in MeOH was stirred at 0 °C for 36 h. The solvent was removed under reduced pressure. ^{1}H-NMR spectral analysis of the reaction mixture revealed a number of products; purification by flash chromatography (Et_2O–petroleum ether 1 : 1, through to Et_2O–MeOH 9 : 1) yielded four products, which are listed in order of elution.

Methyl 5-benzyl-7,9-dimethoxy-1,3,3a,4,5,9b-hexahydroisoxazolo[3′,4′ : 4,5]pyrido[2,3-*d*]pyrimidine-3-carboxylate, 14. A white solid (13.5 mg, 14%), mp 122–123 °C (Et_2O, hexane) (Found C, 59.29; H, 5.55; N, 14.46. $C_{19}H_{22}N_4O_5$ requires C, 59.07; H, 5.70; N, 14.51%); δ_H: 7.24 (5H, m, Ar-H), 4.81 (2H, s, C*H*$_2$Ph), 4.49 (1H, d, *J* 6.01, 9b-H), 4.20 (1H, d, *J* 2.69, 3-H), 3.90 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 3.31 (1H, dd, *J* 12.69 and 4.88, 4-H), 3.08 (1H, m, 4′-H), 2.80 (1H, m, 3a-H), 1.50 (1H, br s, NH). δ_C: 173.31 (C-7), 171.43 (C-9), 164.08 (C-5a), 161.72 (CO_2CH_3), 137.42 (Ar-C), 128.67, 127.48, 127.51 (Ar-CH), 86.17 (C-9a), 80.64 (C-9b), 54.42 (OCH_3), 54.05 (OCH_3), 53.60 (CO_2CH_3), 52.50 (C-3), 51.43 (CH_2Ph), 45.67 (C-4), 43.88 (C-3a). NOEDS results indicate *cis*-geometry at the CB ring junction. Irradiation of 9a-H caused a 9.34% enhancement on the cross ring 3a-H.

Methyl 2-(1-benzyl-8-formyl-7-methoxy-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-*c*]pyrimidin-3-yl)acetate, 12a. A white solid (4.8 mg, 5%), mp 151–153 °C (Et_2O, MeOH) (Found C, 60.45; H, 5.52; N, 11.57. $C_{19}H_{22}N_4O_5$ requires C, 60.05; H, 5.32; N, 11.76%); δ_H: 9.94 (1H, s, CHO), 7.30 (5H, m, Ar-H), 5.26 (1H, d, *J* 15.12, C*H*$_2$Ph), 5.04 (1H, d, *J* 15.13, C*H*$_2$Ph), 4.80 (1H, m, 3-H), 4.04 (3H, s, OCH_3), 3.97 (1H, m, 2-H), 3.65 (3H, s, OCH_3), 3.46 (1H, dd, *J* 11.22 and 4.88, 2′-H), 3.29 (1H, dd, *J* 17.08 and 2.93, C*H*$_2$$CO_2CH_3$), 2.65 (1H, dd, *J* 17.08 and 9.27, C*H*$_2$$CO_2CH_3$); δ_C: 184.71 (CHO), 173.92 (C-7), 170.43 (*C*O_2CH_3), 156.64 (C-5), 153.35 (C-8a), 134.92 (Ar-C), 129.00, 128.34, 128.11 (Ar-CH), 90.26 (C-8), 55.21 (C-3), 54.84 (*C*$H_2$$CO_2CH_3$), 53.96 (*C*$H_2$Ph), 51.99 ($OCH_3$), 51.40 ($OCH_3$), 36.19 (C-2).

Methyl 2-(1-benzyl-8-hydroxyiminomethyl-7-methoxy-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-*c*]pyrimidin-3-yl)acetate, 12b. A white solid (4.8 mg, 5%), mp 186–188 °C (Et_2O, MeOH) (Found C, 58.17; H, 5.00; N, 14.58. $C_{18}H_{20}N_4O_5$ requires C, 58.06; H, 5.38; N, 15.05%); δ_H: 8.55 (1H, s, OH), 7.94 (1H, s, C*H*=N), 7.19 (5H, m, Ar-H), 4.78 (1H, d, *J* 15.63, C*H*$_2$Ph), 4.71 (1H, m, 3-H), 4.65 (1H, d, *J* 15.63, C*H*$_2$Ph), 3.88 (1H, m, 2-H), 3.85 (3H, s, OCH_3), 3.57 (3H, s, OCH_3), 3.37 (1H, dd, *J* 10.99 and 4.39, 2′-H), 3.26 (1H, dd, *J* 16.85 and 3.17, C*H*$_2$$CO_2CH_3$), 2.53 (1H, dd, *J* 16.85 and 9.81, C*H*$_2$$CO_2CH_3$); δ_C: 171.81 (C-7), 170.75 (*C*O_2CH_3), 154.28 (C-8a), 154.04 (C-5), 143.15 (CH=N), 135.08 (Ar-C), 128.93, 128.08, 127.44 (Ar-CH), 79.59 (C-8), 54.95 (OCH_3), 54.92 (C-3), 54.79 (C-2), 51.28 (*C*H_2Ph), 51.06 (CO_2CH_3), 36.03 (*C*$H_2$$CO_2CH_3$).

Title compound 3. A white gum, (R_f 0.1, Et_2O–MeOH 9 : 1) (68 mg, 65%) (Found C, 58.69; H, 5.39; N, 14.87. $C_{19}H_{22}N_4O_5$ requires C, 59.07; H, 5.70; N, 14.51%); δ_H (C_6D_6): 8.21 (1H, s, CHN), 7.10 (5H, m, Ar-H), 4.91 (1H, d, *J* 14.65, C*H*$_2$Ph), 4.40 (2H, m, 7-H, C*H*$_2$Ph), 3.56 (3H, s, OCH_3), 3.27 (3H, s, OCH_3), 3.39 (1H, dd, *J* 15.01 and 5.49, 8-H), 3.27 (3H, s, OCH_3), 3.12 (1H, dd, *J* 16.48 and 5.13, C*H*$_2$$CO_2CH_3$), 3.03 (1H, d, *J* 15.01, 8′-H), 2.33 (1H, dd, *J* 16.48 and 9.15, C*H*$_2$$CO_2CH_3$); δ_C: 170.43 (C-2), 169.21 (C-4), 163.09 (*C*O_2CH_3), 161.09 (C-9a), 136.53 (Ar-C), 131.27 (C-5), 128.60, 127.65, 127.58 (Ar-CH), 86.87 (C-4a), 69.17 (C-7), 54.75 (OCH_3), 54.66 (C-8), 54.00 (OCH_3), 51.96 (CO_2CH_3), 49.79 (*C*H_2Ph), 33.53 (*C*$H_2$$CO_2CH_3$).

2,4-Dimethoxy-6-(prop-2-ynylamino)pyrimidine-5-carbaldehyde oxime 21

To a stirred solution of 6-chloro-5-formyl-2,4-dimethoxypyrimidine (110 mg, 0.54 mmol) in $CHCl_3$ (5 cm^3), propargylamine‡ (37.2 µl, 30 mg, 0.54 mmol) and triethylamine (75.5 µl, 55 mg, 0.54 mmol) were added at 0 °C. The reaction mixture was stirred for 20 h at rt and following solvent evaporation and purification by flash chromatography (petroleum ether–Et_2O, 8 : 2) two new products resulted. 2,4-Dimethoxy-6-(prop-2-ynylamino)pyrimidine-5-carbaldehyde, a white solid (58 mg, 48%), mp 110–111 °C (from petroleum ether, Et_2O) (Found C, 53.81; H, 5.18; N, 18.66. $C_{10}H_{11}N_3O_3$ requires C, 54.30; H, 4.98; N, 19.0%); δ_H: 10.06 (1H, s, CHO), 9.36 (1H, br s, NH), 4.34 (2H, dd, *J* 5.49 and 2.20, NCH_2), 4.03 (3H, s, OCH_3), 4.01 (3H, s, OCH_3), 2.25 (1H, s, C≡CH); δ_C: 187.48 (CHO), 173.55 (C-2), 166.50 (C-4), 163.36 (C-6), 94.54 (C-5), 79.29 (*C*≡CH), 71.40 (C≡*C*H), 55.05 (OCH_3), 54.33 (OCH_3), 30.17 (N*C*H_2); and 2,6-dimethoxy-*N*-(prop-2-ynyl)-5-[(prop-2-ynylimino)methyl]-pyrimidin-4-amine, a white solid (38 mg, 27%), mp 118–119 °C (from petroleum ether, Et_2O) (Found C, 60.07; H, 5.21; N, 21.52. $C_{13}H_{14}N_4O_2$ requires C, 60.47; H, 5.43; N, 21.71%); δ_H: 10.12 (1H, s, NH), 8.83 (1H, d, *J* 1.83, HC=N), 4.34 (2H, dd, *J* 5.49 and 2.56, NCH_2), 4.13 (2H, dd, *J* 2.56 and 1.83, C=N*C*H_2), 4.01 (6H, s, 2 × OCH_3), 2.48 (1H, t, *J* 2.56, C=NCH$_2$C≡C*H*), 2.23 (1H, t, *J* 2.56, C≡CH); δ_C: 170.54 (C-2), 164.72 (C-4), 162.72 (C-6), 157.97 (HC=N), 90.42 (C-5), 80.52 and 79.59 (2 × *C*≡CH), 74.66 (C=NCH$_2$C≡*C*H), 70.59 (C≡*C*H), 54.58 (OCH_3), 53.99 (OCH_3), 47.02 (C=N*C*H_2), 30.13 (NCH_2).

2,4-Dimethoxy-6-(prop-2-ynylamino)pyrimidine-5-carbaldehyde (170 mg, 0.77 mmol) was stirred in methanol (10 cm^3) with hydroxylamine hydrochloride (64 mg, 0.93 mmol) at rt for 5 min. Pyridine (75 µL, 74 mg, 0.93 mmol) was added and the reaction was stirred at rt for 24 h. The solvent was removed under reduced pressure and the residue dissolved in Et_2O, washed with brine (3 × 25 cm^3) and dried over anhydrous Na_2SO_4; evaporation of the organics afforded the title product which was purified by crystallisation. Compound **21**, a white solid (91 mg, 50%), mp 134–135 °C (from Et_2O) (Found C, 50.92; H, 5.40; N, 22.98. $C_{10}H_{12}N_4O_3$ requires C, 50.84; H, 5.12; N, 23.27%); δ_H (d_6-DMSO): 8.47 (1H, s, CHN), 8.14 (1H, br s, NH/OH), 6.97 (1H, s, NH/OH), 4.35 (2H, dd, *J* 5.13 and 2.56, NCH_2), 3.97 (3H, s, OCH_3), 3.49 (3H, s, OCH_3), 2.24 (1H, s, C≡CH); δ_C (DMSO): 168.28 (C-2), 163.52 (C-4), 160.51 (C-6), 143.31 (CHN), 86.59 (C-5), 80.85 (*C*≡CH), 73.68 (C≡*C*H), 54.51 (OCH_3), 53.94 (OCH_3), 29.95 (NCH_2).

Methyl 2-(5-benzyl-1,3-dimethoxy-11-methyl-10,12-dioxo-6,7,9a,10,11,12,12a,12b-octahydro-5*H*-pyrimido[5,4-*f*′]pyrrolo-[3′,4′ : 4,5]isoxazolo[2,3-*d*][1,4]diazepin-7-yl)acetate, 22

To a solution of **3a** (100 mg, 0.26 mmol) in THF (5 cm^3) was added *N*-methylmaleimide (34.5 mg, 0.31 mmol). The solution was stirred at rt for 24 h. The solvent was then removed under reduced pressure and the crude reaction mixture purified by flash chromatography (Et_2O–petroleum ether, 1 : 1). The title

‡ Propargyl = prop-2-ynyl.

compound **22** was isolated as a white solid (90 mg, 73%), mp 144–145 °C (Et_2O) (Found C, 57.84; H, 5.35; N, 14.02. $C_{24}H_{27}N_5O_7$ requires C, 57.95; H, 5.43; N, 14.08%); δ_H (C_6D_6): 7.09 (5H, m, Ar-H), 4.72 (1H, br s, 12b-H), 4.64 (1H, d, *J* 15.61, C*H*$_2$Ph), 4.47 (1H, d, *J* 6.83, 9a-H), 4.21 (1H, d, *J* 15.61, C*H*$_2$Ph), 3.72 (1H, d, *J* 6.83, 12a-H), 3.57 (4H, s, OCH_3, 7-H), 3.50 (3H, s, OCH_3), 3.10 (3H, s, CO_2CH_3), 3.03 (1H, dd, *J* 13.66 and 9.76, 6-H), 2.81 (1H, d, *J* 13.66, 6′-H), 2.69 (3H, s, NCH_3), 2.61 (1H, dd, *J* 15.61 and 3.90, C*H*$_2CO_2CH_3$), 1.94 (1H, dd, *J* 15.61 and 8.78, C*H*$_2CO_2CH_3$); δ_C (C_6D_6): 175.97 (C-10), 173.76 (C-12), 170.11 (C-3), 169.39 (C-1), 165.82 (*C*O_2CH_3), 164.00 (C-4a), 137.70 (Ar-C), 128.59, 127.87, 127.27 (Ar-CH), 88.12 (C-12c), 76.96 (C-9a), 62.82 (C-12b), 57.17 (C-7), 53.90 (CH_2Ph), 53.69 (OCH_3), 53.35 (OCH_3), 52.46 (C-12a), 52.08 (C-6), 50.80 (CO_2CH_3), 36.96 (*C*$H_2CO_2CH_3$), 24.31 (N-CH_3). Irradiation of 12b-H caused the following enhancements: 6.04% on 12a-H, 1.38% on 7-H and 5.34% on 6-H. Irradiation of 6-H caused 16.68% enhancement on 6′-H, 13.82% on 12b-H, 1.91% on 7-H, 1.4% on C*H*$_2CO_2CH_3$ (1.97 ppm) and 0.91% on C*H*$_2$Ph (4.41 ppm).

Methyl 2-(10-acetyl-5-benzyl-1,3-dimethoxy-5,6,7,10,11,11a-hexahydroisoxazolo[2,3-*d*]pyrimido[5,4-*f*][1,4]diazepin-7-yl)-acetates, 23–25 and methyl 2-(11-acetyl-5-benzyl-1,3-dimethoxy-5,6,7,10,11,11a-hexahydroisoxazolo[2,3-*d*]pyrimido[5,4-*f*][1,4]-diazepin-7-yl)acetate, 26

To a solution of **3a** (130 mg, 0.34 mmol) in THF (5 cm^3) was added methyl vinyl ketone (28 mg, 0.40 mmol). The resulting solution was stirred at rt for 3 d. TLC analysis indicated the presence of four new compounds and unreacted nitrone. Purification by flash chromatography (hexane–Et_2O, 3 : 2) followed by crystallisation (hexane, Et_2O) afforded samples of each cycloadduct, the isolated yield of which is based on 53% nitrone consumption.

Adduct 23. A white solid (17 mg, 23%), mp 111–113 °C (Found C, 60.39; H, 5.67; N, 11.90. $C_{23}H_{28}N_4O_6$ requires C, 60.50; H, 6.14; N, 12.30%); δ_H: 7.22 (5H, m, Ar-H), 4.84 (1H, d, *J* 15.61, CH_2Ph), 4.67 (1H, d, *J* 15.61, CH_2Ph), 4.46 (1H, m, 11a-H), 4.28 (1H, m, 10-H), 3.85 (3H, s, OCH_3), 3.77 (4H, br s, OCH_3, 7-H), 3.54 (3H, s, OCH_3), 3.35 (1H, dd, *J* 14.64 and 3.90, 6-H), 2.91 (3H, m, 6′-H, C*H*$_2CO_2CH_3$, 11-H), 2.17 (3H, s, CH_3), 2.11 (1H, m, 11′-H), 2.06 (1H, dd, *J* 15.61 and 7.81, C*H*$_2CO_2CH_3$); δ_C: 203.00 (*C*OCH_3), 171.96 (C-3), 169.71 (C-1), 165.12 (*C*O_2CH_3), 162.41 (C-4a), 138.27 (Ar-C), 128.46, 127.91, 127.25 (Ar-CH), 91.96 (C-11b), 81.18 (C-10), 58.32 (C-11a), 56.92 (C-7), 54.33 (OCH_3), 53.88 (OCH_3), 53.50 (*C*H_2Ph), 52.95 (C-6), 51.74 (CO_2CH_3), 39.23 (C-11), 33.44 (*C*$H_2CO_2CH_3$), 25.96 (CO*C*H_3).

Adduct 24. An 'off-white' solid (9 mg, 12%), mp 114–115 °C (Found C, 60.06; H, 5.64; N, 12.13. $C_{23}H_{28}N_4O_6$ requires C, 60.50; H, 6.14; N, 12.30%); δ_H: 7.22 (5H, m, Ar-H), 4.84 (1H, d, *J* 15.13, CH_2Ph), 4.66 (2H, m, CH_2Ph, 11a-H), 4.49 (1H, dd, *J* 9.76 and 4.88, 10-H), 3.86 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.52 (4H, br s, OCH_3, 7-H), 3.19 (1H, d, *J* 14.15, 6-H), 3.05 (1H, m, 6′-H), 2.76 (1H, dd, *J* 15.61 and 4.88, C*H*$_2CO_2CH_3$), 2.56 (1H, m, 11-H), 2.39 (1H, m, 11′-H), 2.20 (3H, s, CH_3), 2.12 (1H, m, C*H*$_2CO_2CH_3$); δ_C: 209.32 (*C*OCH_3), 171.74 (C-3), 170.00 (C-1), 165.37 (*C*O_2CH_3), 162.87 (C-4a), 138.07 (Ar-C), 128.60, 128.01, 127.37 (Ar-CH), 90.09 (C-11b), 81.52 (C-10), 59.05 (C-11a), 58.33 (C-7), 54.43 (OCH_3, *C*H_2Ph), 54.30 (OCH_3), 52.94 (C-6), 42.80 (C-11), 51.79 (CO_2CH_3), 36.76 (*C*$H_2CO_2CH_3$), 26.49 (CO*C*H_3).

Adduct 25. A white solid (15 mg, 18%), mp 108–110 °C (Found C, 60.22; H, 6.32; N, 12.63. $C_{23}H_{28}N_4O_6$ requires C, 60.50; H, 6.14; N, 12.30%); δ_H: 7.20 (5H, m, Ar-H), 5.02 (1H, d, *J* 15.38, C*H*$_2$Ph), 4.59 (1H, d, *J* 15.38, C*H*$_2$Ph), 4.18 (1H, m, 10-H), 4.02 (1H, m, 11a-H), 3.73 (3H, s, OCH_3), 3.61 (3H, s, OCH_3), 3.45 (3H, s, OCH_3), 3.34 (4H, m, 11-H, 7-H, 6-H, 6′-H), 2.95 (1H, br d, C*H*$_2CO_2CH_3$), 2.44 (1H, dd, *J* 9.77 and 15.87, C*H*$_2CO_2CH_3$), 2.18 (3H, s, CH_3), 2.15 (1H, m, 11′-H); δ_C: 213.12 (*C*OCH_3), 171.94 (C-3), 169.56 (C-1), 165.57 (*C*O_2CH_3), 162.09 (C-4a), 138.35 (Ar-C), 128.47, 127.95, 127.23 (Ar-CH), 93.22 (C-11b), 79.55 (C-10), 63.12 (C-11a), 61.04 (C-7), 54.33 (OCH_3), 53.81 (OCH_3, *C*H_2Ph), 51.69 (CO_2CH_3), 50.46 (C-6), 42.23 (C-11), 36.83 (*C*$H_2CO_2CH_3$), 25.54 (CO*C*H_3).

Adduct 26. A white solid (30 mg, 41%), mp 127–128 °C (Found C, 60.05; H, 6.02; N, 12.11. $C_{23}H_{28}N_4O_6$ requires C, 60.50; H, 6.14; N, 12.30%); δ_H (−19.9 °C): 7.16 (5H, m, Ar-H), 5.45 (1H, d, *J* 15.13, CH_2Ph), 4.58 (1H, d, *J* 7.33, 11a-H), 4.27 (1H, d, *J* 15.14, CH_2Ph), 3.96 (1H, m, 10-H), 3.79 (3H, s, OCH_3), 3.72 (4H, br s, OCH_3, 10′-H), 3.61 (3H, s, OCH_3), 3.39 (4H, m, 7-H, 11-H, 6-H, 6′-H), 2.97 (1H, m, C*H*$_2CO_2CH_3$), 2.57 (1H, m, C*H*$_2CO_2CH_3$), 2.23 (3H, s, $COCH_3$); δ_C (C_6D_6): 205.01 (CO_2CH_3), 171.76 (C-3), 168.55 (C-1), 165.82 (*C*O_2CH_3), 162.18 (C-4a), 137.91 (Ar-C), 128.50, 127.95, 127.27 (Ar-CH), 92.99 (C-11b), 67.85 (C-10), 62.93 (C-11), 62.36 (C-11a), 54.33 (CH_2Ph), 54.01 (C-7), 53.55 (OCH_3), 51.64 (OCH_3, CO_2CH_3), 50.00 (C-6), 36.87 ($CH_2CO_2CH_3$), 29.23 (CO*C*H_3).

Methyl 2-(5-benzyl-11-phenylsulfonyl-1,3-dimethoxy-5,6,7,10,11,11a-hexahydroisoxazolo[2,3-*d*]pyrimido[5,4-*f*][1,4]diazepin-7-yl)acetates, 31 and 32

To a solution of **3a** (100 mg, 0.26 mmol) in THF (5 cm^3) was added phenyl vinyl sulfone (28 mg, 0.52 mmol). The resulting mixture was stirred at rt for 3 d after which TLC analysis indicated the presence of two new adducts and some starting nitrone. Purification by flash chromatography (hexane–Et_2O, 3 : 7) followed by crystallisation (hexane, Et_2O) gave the separated products. The isolated yield of each adduct is based on 61% conversion of nitrone.

Adduct 31. A white solid (50 mg, 57%), mp 139–140 °C (Found C, 58.48; H, 5.39; N, 10.54. $C_{27}H_{30}N_4O_7S$ requires C, 58.48; H, 5.42; N, 10.11%); δ_H: 7.42 (10H, m, Ar-H), 5.21 (1H, br s, 11a-H), 4.76 (1H, d, *J* 15.01, C*H*$_2$Ph), 4.60 (1H, d, *J* 15.01, C*H*$_2$Ph), 4.43 (3H, m, 10-H, 10′-H, 11-H), 3.91 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.56 (3H, s, OCH_3), 3.43 (1H, m, 7-H), 3.26 (1H, br d, 6-H), 2.92 (1H, m, 6′-H), 2.69 (1H, dd, *J* 16.48 and 4.39, C*H*$_2CO_2CH_3$), 2.10 (1H, dd, *J* 16.48 and 8.06, C*H*$_2CO_2CH_3$); δ_C: 171.51 (C-3), 169.94 (C-1), 166.72 (*C*O_2CH_3), 163.11 (C-4a), 138.23 (Ar-C-S), 138.01 (Ar-C), 133.64, 129.05, 128.67, 128.42, 127.87, 127.61 (Ar-CH), 87.91 (C-11b), 67.36 (C-11), 66.34 (C-10), 60.99 (C-11a), 58.51 (C-7), 54.58 (*C*H_2Ph), 54.41 (OCH_3), 54.24 (OCH_3), 53.90 (C-6), 51.82 (CO_2CH_3), 36.88 (*C*$H_2CO_2CH_3$). Irradiation of 7-H caused the following enhancements: 3.77% on C*H*$_2CO_2CH_3$ (2.69 ppm), 2.18% on 6-H, 1.07% on 11a-H. Irradiation of 11a-H caused a 3.59% enhancement on Ar-H, 0.78% on 7-H, 1.19% on 6-H and 0.38% on C*H*$_2CO_2CH_3$ (2.10 ppm).

Adduct 32. A white solid (30 mg, 34%), mp 158–159 °C (Et_2O, hexane) (Found C, 58.59; H, 5.18; N, 9.88. $C_{27}H_{30}N_4O_7S$ requires C, 58.48; H, 5.42; N, 10.11%); δ_H (C_6D_6): 7.19 (10H, m, Ar-H), 5.36 (1H, d, *J* 8.79, 11a-H), 5.15 (1H, d, *J* 15.38, C*H*$_2$Ph), 4.86 (1H, d, *J* 15.74, C*H*$_2$Ph), 4.63 (2H, m, 10-H, 7-H), 4.34 (1H m, 11-H), 3.91 (1H, m, 10′-H), 3.50 (3H, s, OCH_3), 3.37 (3H, s, OCH_3), 3.32 (4H, m, OCH_3, 6-H), 2.75 (2H, m, 2′-H, C*H*$_2CO_2CH_3$), 2.04 (1H, dd, *J* 15.61 and 6.84, C*H*$_2CO_2CH_3$); δ_C: 172.10 (C-3), 170.58 (C-1), 165.52 (*C*O_2CH_3), 163.50 (C-4a), 140.77 (Ar-C-S), 139.68 (Ar-C), 133.27, 129.18, 128.99, 128.33, 128.00, 127.77 (Ar-CH), 86.54 (C-11b), 70.15 (C-11), 66.30 (C-10), 63.70 (C-11a), 58.40 (C-7), 55.50 (*C*H_2Ph), 54.22 (OCH_3, OCH_3), 53.56 (C-6), 51.62 (CO_2CH_3), 38.03 (*C*$H_2CO_2CH_3$). Irradiation of 10′-H caused a 25.47% enhancement on

10-H, and 10.76% on 11-H. Irradiation of 11-H caused a 15.98% enhancement on 11a-H, 4.76% on 10′-H and 7.49% on Ar-H.

Attempted preparation of dimethyl 5-benzyl-1,3-dimethoxy-7-(2-methoxy-2-oxoethyl)-5,6,7,10,11,11a-hexahydroisoxazolo[2,3-*d*]-pyrimido[5,4-*f*][1,4]diazepine-10,11-dicarboxylate 33

To a solution of **3a** (200 mg, 0.52 mmol) in THF (5 cm^3) at rt was added dimethyl fumarate (368 mg, 2.59 mmol). The resulting solution was stirred for 24 h. Purification by flash chromatography (hexane–Et_2O, 1 : 1) achieved isolation of the unstable product. A low temperature ^1H NMR spectrum revealed signals characteristic of **33**, a white solid; δ_H (toluene-d_8, −60 °C): 7.96 (5H, m, Ar-H), 5.19 (1H, d, *J* 15.13, CH_2Ph), 4.90 (1H, d, *J* 7.38, 11a-H), 4.07 (2H, m, CH_2Ph, 11-H), 3.91 (1H, d, *J* 2.93, 10-H), 3.60 (3H, s, OCH_3), 3.45 (4H, m, OCH_3, 7-H), 3.39 (4H, m, CO_2CH_3, 6-H), 3.21 (3H, s, CO_2CH_3), 3.09 (3H, s, CO_2CH_3), 3.05 (1H, br d, 6′-H), 2.78 (1H, dd, *J* 12.61 and 10.73, $CH_2CO_2CH_3$), 2.59 (1H, br d, $CH_2CO_2CH_3$). The cycloadduct was too unstable to provide ^{13}C NMR or any further analytical data.

Reaction of 3a with dimethyl acetylenedicarboxylate

To a solution of **3a** (100 mg, 0.26 mmol) in THF (5 cm^3) was added dimethyl acetylenedicarboxylate (44.3 mg, 47 μl, 0.31 mmol). The solution was stirred at 0 °C for 24 h. The solvent was removed under reduced pressure and the crude product purified by flash chromatography (Et_2O–petroleum ether, 9 : 1); two products were isolated.

Dimethyl 5-benzyl-1,3-dimethoxy-7-(2-methoxy-2-oxoethyl)-5,6,7,11a-tetrahydroisoxazolo[2,3-*d*]pyrimido[5,4-*f*][1,4]diazepine-10,11-dicarboxylate, 37a. Yield 10 mg, 7%; δ_H: 7.27 (5H, m, Ar-H), 5.17 (1H, d, *J* 14.89, CH_2Ph), 4.67 (1H, s, 11a-H), 4.50 (1H, d, *J* 14.89, CH_2Ph), 4.02 (1H, m, 7-H), 3.96 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 3.92 (3H, s, CO_2CH_3), 3.64 (3H, s, CO_2CH_3), 3.55 (3H, s, CO_2CH_3), 3.48 (1H, m, 6-H), 3.24 (1H, br d, 6′-H), 2.40 (1H, dd, *J* 16.11 and 6.59, $CH_2CO_2CH_3$), 2.15 (1H, dd, *J* 16.11 and 7.32, $CH_2CO_2CH_3$).

Methyl 2-(8-benzyl-2,4-dimethoxy-5,6,7,8-tetrahydropteridin-6-yl)acetate, 43. A white solid (9 mg, 10%), mp 115–116 °C (Et_2O, hexane) (Found C, 60.40; H, 6.29; N, 15.70. $C_{18}H_{22}N_4O_4$ requires C, 60.32; H, 6.19; N, 15.63%); δ_H (C_6D_6): 7.12 (5H, m, Ar-H), 4.67 (2H, s, CH_2Ph), 4.19 (1H, br s, NH), 3.74 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.37 (1H, m, 6-H), 3.23 (3H, s, CO_2CH_3), 2.85 (1H, dd, *J* 11.35 and 2.93, 7-H), 2.73 (1H, dd, *J* 11.35 and 7.32, 7′-H), 2.03 (1H, dd, *J* 16.84 and 9.15, $CH_2CO_2CH_3$), 1.82 (1H, dd, *J* 16.84 and 3.66, $CH_2CO_2CH_3$); δ_C (C_6D_6): 171.69 (C-2), 158.19 (CO_2CH_3), 157.42 (C-4), 152.12 (C-8a), 138.74 (Ar-C), 128.76, 128.25, 127.41 (Ar-CH), 104.44 (C-4a), 53.82 (OCH_3), 53.40 (OCH_3), 51.15 (CO_2CH_3), 50.85 (C-7), 50.51 (CH_2Ph), 45.33 (C-6), 38.48 ($CH_2CO_2CH_3$).

1-(4-Chloro-2,6-dimethoxypyrimidin-5-yl)ethanone 6b

1-(6-Chloro-2,4-dimethoxypyrimidin-5-yl)ethanol[22] (0.9 g, 4.12 mmol) was dissolved in CH_2Cl_2 (10 cm^3) and added to a stirred suspension of freshly prepared pyrimidinium chlorochromate (4.44 g, 20.6 mmol) in CH_2Cl_2. The resulting mixture was left to stir at rt for 6 h. Anhydrous Et_2O (20 cm^3) was added to the mixture before filtration through Celite. The insoluble residue was washed three times with anhydrous Et_2O and the washings were also passed through Celite. The organic portions were combined and solvent was removed under reduced pressure; the pure product was crystallised. Title compound **6b** was obtained as a white solid (0.78 mg, 87%), mp 51–52 °C (petroleum ether) (Found C, 44.21; H, 3.75; N, 12.72. $C_8H_9N_2ClO_3$ requires C, 44.3; H, 4.20; N, 12.9%); δ_H: 4.00 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 2.49 (3H, s, CH_3); δ_C: 197.43 (C=O), 168.94 (C-2), 163.84 (C-6), 157.64 (C-4), 114.89 (C-5), 55.65 (OCH_3), 55.14 (OCH_3), 31.63 (CH_3).

Methyl (*E*)-4-[(5-acetyl-2,6-dimethoxypyrimidin-4-yl)(benzyl)-amino]but-2-enoate 5b

To a stirred solution of **6b** (150 mg, 0.69 mmol) in chloroform (7 cm^3), **7** (142 mg, 0.69 mmol) and NEt_3 (0.19 cm^3, 139.6 mg, 1.38 mmol) were added at 0 °C. The reaction mixture was stirred for 3 d at rt The crude mixture was washed with brine (3 × 50 cm^3), dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Purification by flash chromatography (petroleum ether–Et_2O, 2 : 3) afforded the title compound **5b** as a white solid (230 mg, 82%), mp 84–85 °C (Et_2O, hexane) (Found C, 62.60; H, 6.32; N, 10.52. $C_{20}H_{23}N_3O_5$ requires C, 62.34; H, 5.97; N, 10.91%); δ_H: 7.18 (5H, m, Ar-H), 6.79 (1H, m, 3′-H), 5.86 (1H, d, *J* 15.63, 2′-H), 4.47 (2H, s, CH_2Ph), 4.13 (2H, dd, *J* 5.32 and 1.71, 4-H, 4′-H), 3.88 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.64 (3H, s, OCH_3), 2.27 (3H, s, CH_3); δ_C: 200.36 (C=O), 170.47 (C-2), 166.44 (C-6), 163.21 (CO_2CH_3), 143.47 (C-3′), 143.43 (C-4), 136.38 (Ar-C), 128.73, 127.59, 127.55 (Ar-CH), 122.62 (C-2′), 99.23 (C-5), 54.60 (OCH_3), 54.30 (OCH_3), 54.30 (OCH_3), 54.18 (CH_2Ph), 51.67 (CO_2CH_3), 50.44 (C-4′), 32.82 (CH_3).

9-Benzyl-2,4-dimethoxy-7-(2-methoxy-2-oxoethyl)-5-methyl-8,9-dihydro-7*H*-pyrimido[4,5-*e*][1,4]diazepin-6-ium-6-olate 3b

A solution of **5b** (100 mg, 0.26 mmol) in pyridine (2 cm^3, 24.76 mmol) was stirred at 22 °C for 5 minutes. Hydroxylamine hydrochloride (90 mg, 1.3 mmol) was added and stirring continued for 48 h. The pyridine was removed by evaporation under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with brine (3 × 25 cm^3) and dried over anhydrous Na_2SO_4. The CH_2Cl_2 was removed by evaporation under reduced pressure. Purification by flash chromatography (Et_2O–MeOH, 99 : 1) afforded three new products which are described in order of elution.

Methyl 2-(8-acetyl-1-benzyl-7-methoxy-5-oxo-1,2,3,5-tetrahydroimidazo[1,2-*c*]pyrimidin-3-yl)acetate, 12c. Yield 24 mg, 25%, mp 134–135 °C (Et_2O, MeOH) (Found C, 61.92; H, 5.67; N, 10.59. $C_{19}H_{21}O_5N_3$ requires C, 62.30; H, 5.98; N, 10.90%); δ_H: 7.36 (3H, m, Ar-H), 7.12 (2H, d, *J* 6.59, Ar-H), 4.84 (1H, m, 3-H), 4.51 (2H, m, CH_2Ph), 4.14 (1H, m, 2-H), 3.96 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 3.61 (1H, dd, *J* 10.99 and 4.64, 2′-H), 3.43 (1H, dd, *J* 16.85 and 3.17, $CH_2CO_2CH_3$), 2.68 (1H, dd, *J* 16.85 and 9.77, $CH_2CO_2CH_3$), 2.13 (3H, s, CH_3); δ_C: 196.39 (C=O), 170.88 (C-7), 170.62 (CO_2CH_3), 155.29 (C-5), 153.26 (C-8a), 134.11 (Ar-C), 128.97, 128.08, 127.31 (Ar-CH), 91.90 (C-8), 56.41 (C-2), 54.79 (CH_2Ph), 52.20 (OCH_3), 51.95 (C-3), 50.70 (CO_2CH_3), 36.20 ($CH_2CO_2CH_3$), 32.08 (CH_3).

Methyl 2-(8-acetyl-1-benzyl-7-methoxy-5-hydroxyimino-1,2,3,5-tetrahydroimidazo[1,2-*c*]pyrimidin-3-yl)acetate 39. Yield 23 mg, 24%, mp 110–111 °C (Et_2O) (Found C, 59.21; H, 6.06; N, 14.22. $C_{19}H_{22}O_5N_4$ requires C, 59.07; H, 5.70; N, 14.51%); δ_H: 7.42 (1H, s, OH), 7.25 (3H, m, Ar-H), 7.11 (2H, d, *J* 6.96, Ar-H), 4.48 (3H, m, CH_2Ph, 3-H), 4.01 (1H, t, 2-H), 3.89 (3H, s, OCH_3), 3.59 (3H, s, OCH_3), 3.47 (2H, m, 2′-H, $CH_2CO_2CH_3$), 2.51 (1H, dd, *J* 16.84 and 9.52, $CH_2CO_2CH_3$), 2.15 (3H, s, CH_3); δ_C: 194.12 (C=O), 170.81 (C-7), 167.07 (CO_2CH_3), 157.53 (C-8a), 147.24 (C-5), 134.67 (Ar-C), 128.98, 128.18, 127.80 (Ar-CH), 89.03 (C-8), 56.46 (C-2), 54.47 (OCH_3), 53.20 (CH_2Ph), 52.01 (C-3), 50.61 (CO_2CH_3), 35.15 ($CH_2CO_2CH_3$), 32.35 (CH_3); *m*/*z* 387 ($M^+ + 1$), 357, 314, 287, 271, 91 (CH_2Ph), 77 (Ph), 65, 59 (CO_2CH_3).

Title compound 3b. A yellow oil (R_f 0.15 with Et_2O–MeOH 9 : 1) (49 mg, 49%) (Found C, 60.33; H, 5.87; N, 13.61. $C_{20}H_{24}$-

N_4O_5 requires C, 60.00; H, 6.00; N, 14.00%); δ_H: 7.28 (5H, m, Ar-H), 5.06 (1H, d, *J* 15.38, CH_2Ph), 4.80 (1H, m, 7-H), 4.75 (1H, d, *J* 15.38, CH_2Ph), 3.99 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.83 (1H, dd, *J* 12.82 and 9.15, 8-H), 3.62 (3H, s, OCH_3), 3.53 (1H, d, *J* 12.82, 8′-H), 3.17 (1H, dd, *J* 16.84 and 8.06, C$H_2CO_2CH_3$), 2.42 (1H, dd, *J* 16.48 and 5.86, CH_2CO_2-CH_3); δ_C: 170.62 (C-2), 169.43 (C-4), 163.70 (*C*O_2CH_3), 159.24 (C-9a), 140.82 (Ar-C), 136.61 (C-5), 128.63, 127.99, 127.44 (Ar-CH), 90.46 (C-4a), 62.44 (C-7), 57.04 (C-8), 54.58 (OCH_3), 54.28 (OCH_3), 53.99 (*C*H_2Ph), 51.95 (CO_2CH_3), 33.27 (*C*$H_2CO_2CH_3$), 19.64 (CH_3).

Methyl 2-(9-benzyl-2,4-dimethoxy-5-oxo-6,7,8,9-tetrahydro-5*H*-pyrimido[4,5-*b*]azepin-7-yl)acetate, 42

A solution of **5b** (100 mg, 0.26 mmol) was heated to 40 °C in MeOH (10 cm^3) for 10 h. Following solvent evaporation, purification by flash chromatography (Et_2O–MeOH, 99 : 1) afforded the pure products. Isolated yields were calculated based on 80% conversion of starting material. Title compound **42**, a white solid (59 mg, 74%), mp 98–99 °C (from Et_2O, MeOH) (Found C, 61.92; H, 5.67; N, 10.59. $C_{20}H_{23}N_3O_5$ requires C, 62.30; H, 5.98; N, 10.90%); δ_H: 7.31 (5H, m, Ar-H), 5.23 (1H, d, *J* 15.13, CH_2Ph), 4.86 (1H, d, *J* 15.13, CH_2Ph), 4.02 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 3.48 (1H, dd, *J* 14.64 and 4.39, 2-H), 3.18 (1H, dd, *J* 14.64 and 8.29, 2′-H), 2.89 (2H, m, 3-H, 4-H), 2.41 (2H, m, 4′-H, C$H_2CO_2CH_3$), 2.27 (1H, dd, *J* 16.11 and 7.81, C$H_2CO_2CH_3$); δ_C: 196.05 (C-5), 171.94 (C-8), 169.82 (C-6), 168.75 (*C*O_2CH_3), 163.32 (C-9a), 137.46 (Ar-C), 128.71, 127.87, 127.70 (Ar-CH), 97.68 (C-5a), 55.22 (*C*H_2Ph), 54.79 (OCH_3, OCH_3), 53.78 (C-2), 51.78 (CO_2CH_3), 47.45 (C-4), 40.06 (C-3), 36.88 (*C*$H_2CO_2CH_3$). Imidazopyrimidine **12c** (20 mg, 25%) was also isolated, NMR data agree with that reported above.

Dimethyl 5-benzyl-1,3-dimethoxy-7-(2-methoxy-2-oxoethyl)-11a-methyl-5,6,7,11a-tetrahydroisoxazolo[2,3-*d*]pyrimido-[5,4-*f*][1,4]diazepine-10,11-dicarboxylate 37b

A solution of **3b** (130 mg, 0.325 mmol) and dimethyl acetylenedicarboxylate (80 μl, 92 mg, 0.65 mmol) in THF (10 cm^3) was stirred at rt for 72 h. Following solvent evaporation the products were isolated by flash chromatography (petroleum ether–Et_2O, 3 : 2). Title compound **37b** (10 mg, 6%); δ_H (C_6D_6): 7.17 (5H, m, Ar-H), 4.85 (1H, d, *J* 15.01, CH_2Ph), 4.47 (1H, d, *J* 15.01, CH_2Ph), 4.05 (1H, m, 7-H), 3.61 (3H, s, OCH_3), 3.54 (3H, s, OCH_3), 3.48 (1H, dd, *J* 13.18 and 9.52, 6-H), 3.32 (3H, s, CO_2CH_3), 3.24 (3H, s, CO_2CH_3), 3.17 (3H, s, CO_2CH_3), 2.83 (2H, m, 6′-H, C$H_2CO_2CH_3$), 2.17 (3H, s, CH_3), 2.08 (1H, dd, *J* 16.11 and 7.69, C$H_2CO_2CH_3$). Pteridine **43**, a white solid (55 mg, 47%), mp 115–116 °C (from Et_2O, hexane). Data agree with that previously recorded.

Methyl 5-benzyl-1,3-dimethoxy-7-(2-methoxy-2-oxoethyl)-11a-methyl-5,6,7,11a-tetrahydroisoxazolo[2,3-*d*]pyrimido[5,4-*f*]-[1,4]diazepine-11-carboxylate, 37c

Nitrone **3b** (200 mg, 0.5 mmol) was stirred with methyl propiolate (1.5 cm^3, 1.42 g, 16.9 mmol) at rt for 24 h. TLC analysis indicated three new products and some unreacted nitrone. Purification by flash chromatography (hexane–Et_2O, 3 : 2) followed by crystallisation (hexane, Et_2O) gave pure samples of each product. Adducts are described in order of elution and the yield of each is based on 69% conversion of nitrone.

Cycloadduct 37c. A white solid (70 mg, 42%), mp 127–128 °C (Found C, 59.49; H, 5.29; N, 11.27. $C_{24}H_{28}N_4O_7$ requires C, 59.50; H, 5.79; N, 11.57%); δ_H: 7.41 (1H, s, C-10), 7.24 (5H, m, Ar-H), 4.67 (1H, d, *J* 14.65, CH_2Ph), 4.43 (1H, d, *J* 14.65, CH_2Ph), 3.94 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 3.61 (3H, s, CO_2CH_3), 3.60 (4H, br s, CO_2CH_3, 7-H), 3.30 (1H, m, 6-H), 2.73 (2H, m, 6′-H, C$H_2CO_2CH_3$), 2.26 (1H, dd, *J* 16.11 and 8.06, C$H_2CO_2CH_3$), 1.84 (3H, s, CH_3); *m*/*z* 484 (M^+, 100%), 385, 358, 193, 91 (CH_2Ph).

Table 2 Crystal data and structure refinement for **37c**

Formula	$C_{24}H_{28}N_4O_7$
Formula weight	484.50
Temperature/K	293(2)
Crystal system	Triclinic
Space group	$P\bar{1}$
Unit cell dimensions	
a/Å	10.628(5)
b/Å	11.108(3)
c/Å	11.442(5)
α/°	71.62(3)
β/°	74.82(4)
γ/°	85.00(3)
Volume/Å^3	1237.1(9)
Z	2
Absorption coefficient/mm^{-1}	0.097
Reflections collected	5872
Independent reflections	5692 [R(int) = 0.0139]
Reflections observed (>2*σ*)	2718
Data/restraints/parameters	5692/3/641
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0741$ $wR_2 = 0.1800$
R indices (all data)[a]	$R_1 = 0.1290$ $wR_2 = 0.2121$

[a] R indices: $R_1 = [\Sigma||F_o| - |F_c||]/\Sigma|F_o|$ (based on F), $wR_2 = [[\Sigma_w(|F_o^2 - F_c^2|)^2]/[\Sigma_w(F_o^2)^2]]^{1/2}$ (based on F^2); $w = 1/[(\sigma F_o)^2 + (0.1602*P)^2]$.

Methyl (*E*)-3-[8-benzyl-2,4-dimethoxy-6-(2-methoxy-2-oxoethyl)-5,6,7,8-tetrahydropteridin-5-yl]prop-2-enoate, 44. A white solid (39 mg, 23%), mp 108–109 °C (Found C, 59.51; H, 5.49; N, 12.56. $C_{22}H_{26}N_4O_6$ requires C, 59.72; H, 5.92; N, 12.66%); δ_H: 7.50 (1H, d, *J* 13.18, N-C*H*=CH), 7.23 (5H, m, Ar-H), 5.03 (1H, d, *J* 14.65, CH_2Ph), 4.76 (1H, d, *J* 13.18, N-CH=C*H*), 4.51 (1H, d, *J* 14.65, CH_2Ph), 4.12 (1H, m, 6-H), 3.90 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.59 (3H, s, CO_2CH_3), 3.49 (3H, s, CO_2CH_3), 3.40 (1H, dd, *J* 12.45 and 4.03, 7-H), 3.20 (1H, br d, *J* 7′-H), 2.31 (1H, dd, *J* 16.11 and 6.96, C$H_2CO_2CH_3$), 2.14 (1H, dd, *J* 16.11 and 7.32, C$H_2CO_2CH_3$); δ_C: 170.66 (C-2), 169.41 (C-4), 162.79 (C-8a), 160.72 (*C*O_2CH_3), 154.04 (*C*O_2-CH_3), 148.85 (N-*C*H=CH-), 137.09 (Ar-C), 128.60, 128.06, 127.65 (Ar-CH), 96.61 (C-4a), 90.59 (N-CH=*C*H-), 54.59 (OCH_3, OCH_3), 54.13 (CO_2CH_3), 51.92 (*C*O_2CH_3), 51.07 (C-7), 50.80 (C-6), 47.88 (*C*H_2Ph), 34.78 (*C*$H_2CO_2CH_3$); *m*/*z* 442 (M^+, 100%), 411 (M − 31 = CH_2OH), 369 (M − 73 = $CH_2CO_2CH_3$), 278, 193, 149, 104, 91 (CH_2Ph).

Methyl 2-(8-benzyl-2,4-dimethoxy-5,6,7,8-tetrahydropteridin-6-yl)acetate, 43. A white solid (29 mg, 17%), mp 115–116 °C (Et_2O, hexane); NMR data agree with that described above.

X-Ray crystal determination of 37c.§ The structure was solved by direct methods, SHELXS-97,[23] and refined by full matrix least squares using SHELXL-97.[24] SHELX operations were rendered paperless using ORTEX which was also used to obtain the drawings.[25] Data were corrected for Lorentz and polarisation effects but not for absorption. Hydrogen atoms were included in calculated positions with thermal parameters 30% larger than the atom to which they were attached. The non-hydrogen atoms were refined anisotropically. All calculations were performed on a Pentium PC. Crystal data for **37c** are given in Table 2.

Acknowledgements

This work has been supported by an Enterprise Ireland Basic Science Research Grant (SC/96/402) [F. H. and C. B.] and the

§ CCDC reference number 207/509. See http://www.rsc.org/suppdata/p1/b0/b007163n/ for crystallographic files in .cif format.

chemistry departments of The National University of Ireland, Galway and The National University of Ireland, Maynooth.

References

1 D. J. Brown, R. F. Evans, W. B. Cowden and M. D. Fenn, *The Pyrimidines*, Wiley, New York, 1994.
2 S. Bourke and F. Heaney, *Tetrahedron Lett.*, 1995, **36**, 7527; F. Heaney and S. Bourke, *J. Chem. Soc.*, *Perkin Trans. 1*, 1998, 955; F. Heaney, S. Bourke, D. Cunningham and P. McArdle, *J. Chem. Soc.*, *Perkin Trans. 2*, 1998, 547.
3 M. Noguchi, T. Mizukoshi, T. Uchida and Y. Kuroki, *Tetrahedron*, 1996, **52**, 13097; M. Noguchi, T. Mizukoshi and A. Kakehi, *Tetrahedron*, 1996, **52**, 13081; M. Noguchi, H. Yamada, S. Takamura, K. Okada, A. Kakehi and H. Yamamoto, *Tetrahedron*, 2000, **56**, 1299.
4 F. Heaney, S. Bourke, C. Burke, D. Cunningham and P. McArdle, *J. Chem. Soc.*, *Perkin Trans. 1*, 1998, 2255.
5 A. Barco, S. Benetti, G. Spalluto, A. Casolari, G. P. Pollini and V. Zanirato, *J. Org. Chem.*, 1992, **57**, 6279; R. V. Hoffman and B. S. Severns, *J. Org. Chem.*, 1996, **61**, 5567; R. V. Hoffman and H.-O. Kim, *J. Org. Chem.*, 1991, **56**, 1014; H. K. Leung, B. A. Phillips and N. H. Cromwell, *J. Heterocycl. Chem.*, 1976, **13**, 247.
6 J. A. Gregory, A. J. Jennings, G. F. Joiner, F. D. King and S. K. Rahman, *Tetrahedron Lett.*, 1995, **36**, 155.
7 We thank the referee for this suggestion.
8 (*a*) W. Oppolzer and K. Keller, *Tetrahedron Lett.*, 1970, 1117; (*b*) R. Grigg, F. Heaney, J. Markandu, S. Surendrakamar, M. Thornton-Pett and W. J. Warnock, *Tetrahedron*, 1991, **47**, 4007; (*c*) A. Hassner, R. Maurya, A. Padwa and W. H. Bullock, *J. Org. Chem.*, 1991, **56**, 2775; (*d*) E. Falb, Y. Bechor, A. Nudelman, A. Hassner, A. Albeck and H. E. Gottlieb, *J. Org. Chem.*, 1999, **64**, 489 and references therein; (*e*) M. Gotoh, B. Sun, K. Hirayama and M. Noguchi, *Tetrahedron*, 1996, **52**, 887.
9 R. Grigg, J. Markandu, T. Perrior, S. Surendrakumar and W. J. Warnock, *Tetrahedron*, 1992, **48**, 6929.
10 T. Inazumi, K. Yamada, Y. Kuroki, A. Kakehi and M. Noguchi, *J. Chem. Soc.*, *Perkin Trans. 1*, 1994, 557; E. C. Taylor and P. S. Ray, *Heterocycles*, 1991, **32**, 1327; B. Baruah, D. Prajapati, J. S. Sandhu and A. C. Ghosh, *J. Chem. Soc.*, *Perkin Trans. 1*, 1996, 1999.
11 R. Grigg, T. R. Perrior, G. J. Sexton, S. Surendrakumar and T. Suzuki, *J. Chem. Soc.*, *Chem. Commun.*, 1993, 372.
12 D. Lathbury and T. Gallagher, *J. Chem. Soc.*, *Chem. Commun.*, 1986, 1017.
13 (*a*) M. C. Aversa, P. Giannetto, A. Ferlazzo and G. Romeo, *J. Chem. Soc.*, *Perkin Trans. 1*, 1982, 2701; (*b*) N. W. Gilman, P. Rosen, J. V. Earley, C. M. Cook, J. F. Blount and L. J. Todaro, *J. Org. Chem.*, 1993, **58**, 3285; (*c*) J. Messinger and V. Buss, *J. Org. Chem.*, 1992, **57**, 3320; (*d*) T. A. Keating and R. W. Armstrong, *J. Org. Chem.*, 1996, **61**, 8935.
14 J. J. Tufariello, in *1,3-Dipolar Cycloadditions*, ed. A. Padwa, Wiley, New York, 1982, vol. 2, p. 96.
15 M. Burdisso, A. Gamba, R. Gandolfi and R. Oberti, *Tetrahedron*, 1988, **44**, 3735.
16 J. P. Freeman, *Chem. Rev.*, 1983, **83**, 241.
17 N. W. Gilman, P. Rosen, J. V. Earley, C. M. Cook and L. J. Todaro, *J. Am. Chem. Soc.*, 1990, **112**, 3969.
18 M. L. Miller and P. S. Ray, *Tetrahedron*, 1996, **52**, 5739.
19 J. P. Freeman, D. J. Duchamp, C. G. Chidester, G. Slomp, J. Szmuszkovicz and M. Raban, *J. Am. Chem. Soc.*, 1982, **104**, 1380.
20 W. Pfleiderer, in *Comprehensive Heterocyclic Chemistry II*, Vol. Ed. C. A. Ramsden, Series Eds. A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Pergamon Press, Oxford, 1996, Vol. 7, p. 714.
21 N. Ple, A. Tuck, E. Fiquet and G. Queguiner, *J. Heterocycl. Chem.*, 1991, **28**, 283.
22 C. Piancatelli, A. Scettri and M. D'Auria, *Synthesis*, 1982, 245.
23 G. M. Sheldrick, *Acta Crystallogr.*, *Sect. A*, 1990, **46**, 467.
24 G. M. Sheldrick, SHELXL-97, a computer programme for crystal structure determination, University of Göttingen, 1997.
25 P. McArdle, *J. Appl. Crystallogr.*, 1995, **28**, 65.